CONCEPT REVIEW – June 12, 2008

Contract Title: NTP and NIEHS Investigative Research Support Contract

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I. Purpose

The purpose of the proposed contract is to provide scientific support for National Toxicology Program (NTP) and National Institute of Environmental Health Sciences (NIEHS) investigators. At NIEHS, space for laboratory research, housing and dosing of animals, and access to certain technological methods are limited. Many NIEHS and NTP projects require specialized facilities for the conduct of experiments. Therefore, there is a strong need for NTP and NIEHS investigators to have use of offsite laboratory facilities and staff to conduct primary or follow-up investigative research projects in support of the program and institute initiatives. This contract would support projects that are an extension of NIEHS/NTP investigator's research activities that cannot be performed at NIEHS or are not achievable through other NTP or NIEHS contracts.

Project and research support needs vary depending on the investigator and program and institute initiative and by this contract such versatile needs can be met in an efficient and cost-effective means. Anticipated future research support needs include the breeding and housing of Specific Pathogen Free (SPF) or non-SPF animals, temporary housing of NIEHS colonies, characterizing animal models, conducting mechanistic studies, providing necropsy and tissue collection, applying molecular biology assays, and providing data management for the Genetic Alterations in Cancer Database. Other support would include arranging for meetings and workshops and conducting studies in support of NTP initiatives in immunologic, developmental, and reproductive toxicity.

II. Background

The National Toxicology Program (NTP) was established as a cooperative effort within the Department of Health and Human Services to coordinate and manage toxicology testing efforts and provide the scientific information about environmental exposures needed by health and regulatory agencies for sound public health decision-making. The NTP is headquartered at the NIEHS, but also includes the relevant activities at the National Institute for Occupational Safety and Health and the National Center for Toxicological Research. The NIEHS as part of the NIH has a mission is "to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease."

This contract is to continue support for activities that have been available for NTP and NIEHS research investigations since 2003. Prior to 2003, three different longstanding NTP/NIEHS contracts supported such investigations. During the past 4 years, the Molecular Oncology and Toxicology Support contract has provided research support for about 40 of the approximately 60

NIEHS intramural principal investigators and 30 NTP scientists (see partial list of recent manuscripts in Table 3). Specifically, the support was crucial to increasing our understanding, evaluation, and reporting of:

- toxicogenomics data as part of the efforts of the National Center for Toxicogenomics
- phenotypic "anchoring" of genomics data
- genetically altered mice models (i.e. Table 1)
- potential new biomarkers of toxicity (i.e. troponin, lung cancer, and gene transcripts)
- environmental pulmonary disease models (i.e. fibrotic lung diseases, airway disease, and nanoparticle studies)
- applying state-of-the-art imaging modalities in carcinogenesis or teratology studies
- genetic susceptibility to radiation carcinogenesis in p53 deficient mice
- many other projects

III. Objectives

The new contract would support the research needs of NTP and NIEHS as outlined below.

- Provide research support for NTP and other NIEHS investigators to conduct experiments to examine and/or characterize animal models or *in vitro* systems, or to generate tissue samples following treatments under defined protocols. The types of support could include animal dosing (see Table 2 for past studies), conducting in-life observations, performing necropsies, collecting tissues for molecular analysis, conducting molecular analyses and *in vitro* assays, and reporting results.
- Provide expertise and facility to house, breed, and genotype multiple isogenic mouse strains and to perform multistrain and phenotyping studies for NIEHS/NTP investigators.
- Provide housing for both Specific Pathogen Free (SPF) and non-SPF animals.
- Maintain the NTP's Genetic Alterations in Cancer (GAC) database.
- Provide support for meetings/workshops.

IV. Priority

This support contract is considered a high priority because it would support the NIEHS and NTP in providing the best scientific information to protect public health. There is a strong need for NTP and NIEHS investigators to have such research support to conduct primary or follow-up investigative research projects in support of the program and institute initiatives.

Genetically altered mouse models utilized in various studies over the past 5 years under the current contract

eGFP $^{+/-}$
CD34 $^{-/-}$
Gnai2 $^{-/-}$
CYP2E1
Keratin.Cre
CAR
NAG
TRAMP
Tg.AC
Gadd 45
APC^{min}
C57BL/6 Wild Type
Txnip mice
AhR +/-
Trp53 deficient
B6C3F1
C57BL/6J
C57BL/6J-APC^{min}
Scavenger Receptor knockout mice

Selected chemicals/agents administered in various studies over the past 5 years under the current contract

Cyclophosphamide
N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)
Sulindac
Retinoic acid
Acrylamide
dimethylbenz(a)anthracene (DMBA)
Arsenic
Phenobarbital
Diethylnitrosamine (DEN)
2-Butoxyethanol
12-O-tetradecanoylphorbol-13-acetate (TPA)
Dexamethasone
Lipopolysaccharide (LPS)
Nanoparticles (Quantum Dots)
Methylazoxymethanol acetate (MAM)

Selected examples of recent manuscripts/publications supported by this contract

Lobenhofer, E.K., J.T. Auman, P.E. Blackshear, G.A. Boorman, P.R. Bushel, M.L. Cunningham, J.M. Fostel, K. Gerrish, A.N. Heinloth, R.D. Irwin, D.E. Malarkey, B.A. Merrick, S.O. Sieber, C.J. Tucker, S.M. Ward, R.E. Wilson, P. Hurban, R.W. Tennant, and R.S. Paules. 2008. Gene expression response in target organ and whole blood varies as a function of target organ injury phenotype. In Press.

Yamamoto, Y, and Negishi, M. 2008. The anti-apoptotic factor GADD45B is a novel co-activator of the nuclear receptor CAR. Drug. Metab. Disp. In press

Yamamoto Y, Moore R, Flavell RA, Lu B, and Negishi M. 2008. Nuclear receptor CAR represses TNFa-induced cell death by interacting with the anti-apoptotic GADD45B. Submitted.

Huang, L., A.N. Heinloth, Z.-B. Zeng, R.S. Paules, and P.R. Bushel. 2008. Prediction of necrosis as a phenotype from rats exposed to a compendium of hepatotoxicants. Submitted.

Bushel, P.R., A.N. Heinloth, J. Li, L. Huang, J.W. Chou, G.A. Boorman, D.E. Malarkey, C.D. Houle, S.M. Ward, R.E. Wilson, R.D. Fannin, M.W. Russo, P.B. Watkins, R.W. Tennant, and R.S. Paules. 2007. Blood gene expression signatures predict exposure levels. *Proc. Natl. Acad. Sci. U.S.A.* 104, 18211-18216 (Epub November 2, 2007, 10.1073 / pnas.0706987104).

Heinloth, A.N., G.A. Boorman, J.F. Foley, N.D. Flagler, and R.S. Paules. 2007. Gene expression analysis offers unique advantages to histopathology in liver biopsy evaluations in rat. *Toxicol. Pathol*., 35, 276-283.

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Auman, J.T., G.A. Boorman, R.D. Irwin, R.E. Wilson, G.S. Travlos, and R.S. Paules. 2007. Heat map visualization of high-density clinical chemistry data. *Physiol. Genomics.* 31, 352-356 (Epub 2007 July 24; PMID: 17652165).

Trempus, CS, Morris, RJ, Ehinger, M, Elmore, A, Bortner, CD, Ito, M, Cotsarelis, G, Nijhof, J, Peckham, J, Flagler, N, Kissling, G, Humble, MM, King, LC, Adams, LD, Desai, D, Amin, S, and Tennant, RW. 2007. CD34 expression by hair follicle stem cells is required for skin tumor development in mice. Cancer Research. 67(9):4193-4181.

Phillips, JM., Yamamoto, Y, Negishi, M, Maronpot, RR, and Goodman, JI. 2007. Orphan nuclear receptor constitutive active/androstane receptor-mediated alterations of DNA methylation during phenobarbital promotion of liver tumorigenesis. Toxcol. Sci. 96: 72-82.

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